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Applicant	:	Ian Cottrell			
Application No.:		10/800,407	Art Unit No.	:	1623
Filed	:	March 12, 2004	Examiner	:	Elli Peselev
For	:	IMPROVED ANTHELMINTIC FORMULATIONS			

DECLARATION OF IAN COTTRELL, PH.D. UNDER 37 CFR RULE 1.132

I, Ian Cottrell, Ph.D., declare the following:

1. I am an inventor of the subject application and am an employee of the Assignee. I have a Ph.D. in organic chemistry from the University of Edinburgh, Scotland and over thirty years of experience in research and development of specialty chemicals and consumer products. I am familiar with the application, the Final Office Action dated February 23, 2006 and the references cited therein. This Declaration is intended to form part of a response to the February 23, 2006 Office Action.

2. Important embodiments of the invention relates to a solid insecticide formulation containing anthelmintic avermectin such as ivermectin, spray granulated with polyethylene glycol or cellulose, plus other active compositions such as hexahydropyrazinoisoquinolines and anthelmintic pyrimidines such as tetrahydropyrimidines and benzimidazoles such as pyrantel a method of controlling insect infestation in animals with such an insecticide; and a method of preparing an insecticide.

3. Ivermectin is a po ent antiparasitic agent, as disclosed in U.S. Pat. No. 4,199,569, and thus useful in an anthelmintic combination. However, ivermectin is difficult to use in combination with other anthelmintic compounds. Specifically, it is shown below that iverm ectin has a compatibility problem with the presence of other anthelmentic agents present in the invention: pyrantel (pamoate) and praziquantel, even though a solid combination of these compounds is therapeutically desirable.

4. Ivermectin, pyran tel (pamoate), and praziquantel are three of the four active ingredients incorporated into chewable tablets. To investigate the compatibility among thes e three actives, the following compatibility study was performed. An HPLC method was usec in the compatibility study. In th is test, the three actives (ivermectin:pyrantel pamoate:praziqua ntel in a ratio of 1:10:10) are dry mixed. The resulting mixture and each individual active were put on accelerated condition of 130 °F for 1 week, 2 weeks, 3 weeks and 4 weeks. Then the therma lly treated individual actives and the mixture were analyzed using HPLC. To the extent the spec ra of the each individual in the mixture are different from those of each individual itself, for example, peak shift, presence of new peak, peak shrink or disappearance of peak, it indicates a reaction among ivermectin, pyrantel (pamoate), and praziquantel. To the extent there is no change when comparing the spectra of the three actives with those of each individual itself, t ie compatibility of the three ac ives is acceptable.

5. The analytical results of thermally treated ivermectin alone and with antiparasitic mixture samples are listed in Table I and Table II below.

Table 1 Stability of Ivermectin

Time @ Condition	Ivermectin (4.76%)	
	Assay (%)	Red. (%)
Initial	98.22	
1 wk @ 130 °F	99.42	
2 wks @ 130 °F	99.39	
3 wks @ 130 °F	-	
4 wks @ 130 °F	98.47	0

Table 2 Compatibility of Antiparasitic Ingredients Mixture

Time @ Condition	Ivermectin (4.76%)		Praziquantel (47.6%)		Pyrantel Pamoate (47.6%)	
	Assay (%)	Red. (%)	Assay (%)	Red. (%)	Assay (%)	Red. (%)
Initial	4.95		47.41		46.68	
3 wk @ RT	4.59		46.65		47.88	
1 wk @ 130 °F	4.6		47.02		47.65	
2 wks @ 130 °F	4.99		45.44		47.24	
3 wks @ 130 °F	4.6		45.58		46.9	
4 wks @ 130 °F	4.44	10.3	46.14	2.68	47.4	

It can be observed in the Table I that ivermectin itself is very stable under condition of 130 °F for 4 weeks. However, Table II shows that in the presence of the other two antiparasitic agents, praziquantel and pyrantel pamoate, ivermectin decreased about 10.3% from its initial assay. This indicates that ivermectin has a potential stability/compatibility problem in the presence of praziquantel and pyrantel pamoate.

6. In addition to stability, an important objective of the invention was to discover an insecticide containing a high enough concentration of parasiticidally effective material to minimize the size of parasiticide tablets an animal needs to ingest.

7. I have reviewed Mihalik, U.S. Pat. No. 6,340,672 ("Mihalik"). There is nothing in the Mihalik reference to suggest an parasiticide formulation that would satisfy either objective.

Mihalik merely teaches that a combination of anthelmintics would be soluble in a pyrrolidone solvent system. It does not discuss the stability issue or resolve the difficulty of stabilizing ivermectin over time or preventing ivermectin degradation in the presence of other active anthelmintic compounds. Accordingly, it is not a simple matter to create a stable solid formulation combining multiple anthelmintics based on the liquid formulation disclosed in Mihalik.

8. I have reviewed Maxfield et al., U.S. Pat. No. 4,597,969 ("Maxfield"). Maxfield shows that the stabilizing effect is confined to a combination of alginic acid and magnesium hydroxide over a narrow range of concentrations. Beyond this specific combination, the stability of ivermectin drops. Maxfield's teachings would not eliminate the need for filler materials or stabilizers such as alginic acid and magnesium hydroxide. Thus, a person skilled in the art, upon reading Maxfield, would not have thought to spray granulate ivermectin with polyethylene glycol using the method disclosed in the patent (which achieves unexpected stability without requiring the addition of alginic acid, antioxidants, or other stabilizers).

9. In my opinion the alginic acid as disclosed in Maxfield is not a pharmaceutically desirable additive to stabilize ivermectin in the present combination. Using alginic acid in the method disclosed by Maxfield will actually reduces the effectiveness of the combination. Alginic acid, being negatively charged, can bind to positively charged compounds, including the active compound pyrantel, and thus impact the bioavailability of the resulting combination. Thus, it teaches away from the combination. In contrast, polyethylene glycol and cellulose are inert to the other active ingredients. Thus the use of polyethylene glycol or cellulose in the present invention enables a simpler formulation that reduces the risk of deleterious reactions or interactions occurring between the carrier and the anthelmintic ingredients.

10. While Maxfield et al. disclose the addition of polyethylene glycol to ivermectin (column 5, line 62-68), the use of polyethylene glycol in Maxfield is not related to the use of polyethylene glycol here. Polyethylene glycol is used as a lubricant in Maxfield, and is combined with the ivermectin after it is already granulated with alginic acid. Polyethylene glycol achieves the unexpected stabilizing result here when used with ivermectin during the granulation process, which allows the polyethylene glycol to coat and to protect ivermectin before the unstable ivermectin is combined with other potentially incompatible active compounds.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Ian Cottrell, Ph.D.

Dated: 5/23/06